THE UNIVERSITY OF WISCONSIN
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Madison 6

DEPARTMENT OF GENETICS

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Dr. Evelyn Witkin,
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Dear Evelyn-

The Symposium Volume XII having just come out, I had a chance to look over some of your graphs again, and as usual was stimulated to think about the incredibly wide range of toxic compounds which seem to be mutagenic. I agree that the approach you suggested at our last meeting, looking for other mutable systems, may be the best. In that connection, I want to say that I haven't been able to get the same type of non-linear response to dilution of the appearance of biochemical reversions that you describe, not using, of course the same mutants. My experiments were rather casual, but the results were in reasonable conformity with a priori expectations. The suggestion that you are probably using a system which is not adequately deprived of the metabolite required seems to me the most reasonable explanation of your findings, and I would be interested to hear your current opinion. Szilard was,of course, overexcited about, and in addition I received some sly glances from skeptics who thought that the "Witkin" phenomenon devastated recombination in K-12. Secondly, have you been able to induce reverse-mutations in any biochemical mutants. My attempts, again quite casual, have been negative with coli-- but I wouldn't take this statement very seriously. A word of caution about reversions-- I have found several examples now of phenotypic reversions which are not reverse-mutations, but suppressor mutations ala Houlahan & Mitchel

One aspect of bacterial mutation work troubles me considerably. By analogy

but are you necessarily inducing mutations with your chemicals. The lack of a delayed effect (is this so?) in contrast with ultraviolet light and X-rays seems to tie in with the observation that spontaneous mutations are not recovered from resting cells. If I remember correctly, such mutations do occur in sperms and seeds which have been aged. The genetic condition of your microbial population is an unknown, although the cytological studies afford a clue. These observations are consistent with the hypothesis that the manifest (background) variation is only a small fraction of the total variation in control cultures, most of it being masked, let us say, in the di-karyotic condition. Since Robinow's pictures clearly show cells with 4 nuclei, it may be that most of the cell divisions do not segregate out the nuclei. I.E., AB → AABB --→ either AA and BB, or AB & AB. "Conjugate Division" is quite common in other fungi. I use the nuclei as the unit of multiplicity for reasons of economy: much the same would apply to chromatids, gene platelets,etc. Under these conditions, any agent which inhibited the division of a nucleus, or otherwise disrupted it , would appear to have a mutagenic effect: AB→ A. If this be true, it seems to me that it could be approached by studying the effects of your incredible chemical mutagens on X-ray or UV-treated bacteria. The mutagens should have the effect of acceleratin the appearance of "endpoint" mutations induced by the radiation. [As you probably know, X-rays can induce the dissociation (by nuclear "killing") of N. tetraspern ascospores.] Whether you think there is anything to this or not, keep me posted. Best regards,

Joshua